Regional citrate anticoagulation in continuous renal replacement therapy for acute kidney injury

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General introduction and outline of the thesis

Acute kidney injury (AKI) is common in critically ill patients, depending on the definition occurring in 20% of hospitalized patients and as many as two thirds of patients admitted to the intensive care unit (ICU) [1,2]. AKI nowadays is defined using a set of criteria first described in 2004 called the RIFLE (Risk, Injury, Failure, Loss, and End stage) criteria. The RIFLE criteria classify AKI into three groups (Risk, Injury, and Failure) according to relative changes of serum creatinine and urine output [3]. The RIFLE criteria subsequently were modified by the AKI Network (AKIN) in 2007 (Table 1) [4].

The etiology of AKI in the ICU is often multifactorial. AKI and even slight renal function deterioration are associated with increased mortality [2,4]. Basic principals of renal support therefore consist of early detection and prevention of AKI by immediate fluid resuscitation to restore circulating volume (often with the need of vasopressor drugs), avoiding nephrotoxins and, when AKI is severe, initiating renal replacement therapy (RRT). There are many criteria for the initiation of RRT including uncontrolled uraemia, diuretic-resistant volume overload, respiratory distress and multi-organ failure. The appropriate timing of initiation, however, remains a topic of great controversy. In spite of novel techniques of RRT, mortality rates for AKI remain as high as up to 60% [5-7].

Table 1 RIFLE and AKIN criteria for diagnosis and classification of AKI

AKIN	**Urine output**	**Class**	**RIFLE**
Serum creatinine	Both classifications		Serum creatinine
Stage 1 Increase of ≥26.5 µmol/l or increase of 1.5- to 2-fold from baseline	Less than 0.5 ml/kg/h for more than 6 hours	**R**isk	Increase of 1.5 fold from baseline or GFR decrease >25%
Stage 2 Increase of >2- to 3-fold from baseline	Less than 0.5 ml/kg per hour for more than 12 hours	**I**njury	Increase of 2 fold from baseline or GFR decreased >50%
Stage 3 Increase of >3-fold from baseline, or ≥354 µmol/l) with an acute increase of at least 44 µmol/l or on RRT	Less than 0.3 ml/kg/h for 24 hours or anuria for 12 hours	**F**ailure	Increase of 3 fold from baseline, or serum creatinine >354 µmol/l with an acute rise >44 µmol/l) or GFR decreased >75%
		Loss	Complete loss of kidney function >4 weeks
		End stage renal disease	Loss of kidney function >3 months

Novel biomarkers and mediators of AKI

The clinical diagnosis of AKI relies on serum creatinine and urinary output, but these parameters are highly variable and may lack accuracy in non-steady state conditions. Changes in serum creatinine levels lag behind in both renal function loss and recovery and thus are not useful in diagnosing subclinical AKI. In patients with subclinical AKI, ongoing damage may be prevented by appropriate measures. Therefore, urinary and serum biomarkers to predict or detect AKI before the rise of creatinine have been studied intensively. In the last decade, several novel AKI biomarkers have been identified, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1), cystatin C, IL-18, and liver-type fatty acid-binding protein (L-FABP). NGAL, one of the neutrophil secondary granule proteins [8], is probably the most studied marker. NGAL is expressed in a variety of human tissues, including lung, liver and kidney, in various pathologic states. NGAL is rapidly induced in distal tubular segments of injured nephrons upon stress [9]. Urine NGAL is derived predominantly from epithelial cells of the distal nephron, although a fraction may come from the systemic pool escaping reabsorption in the proximal tubule due to its injury. Plasma NGAL originates not only from the damaged kidneys (via tubular back-leak) but also from extrarenal organs. Urinary and plasma levels are helpful in predicting the occurrence of AKI [10-13], in prediction of severity of AKI [12-15] and AKI-related outcomes, such as need for renal replacement therapy (RRT) and mortality [11-13,15-18]. Also, levels of NGAL are associated with disease severity and its levels are more profoundly elevated during sepsis [11,13,17,19-21]. Other novel mediators have been described to be implicated in the development of AKI, for instance in the course of sepsis. One of these mediators is TNF-associated weak inducer of apoptosis (TWEAK), a member of the super tumor necrosis factor (TNF) family, that activates the Fn14 receptor. TWEAK is broadly expressed and can be found at high levels in the pancreas, intestine, heart, brain, lung, ovary, vasculature, and skeletal muscle, and at lower levels in the liver and kidney. TWEAK and Fn14 are constitutively expressed at low levels in normal kidneys. Potential local sources of kidney TWEAK include infiltrating monocytes/macrophages and T lymphocytes, and resident cells such as tubular and mesangial cells. TWEAK contributes to kidney inflammation by promoting chemokine secretion by renal cells through canonical and non-canonical Nuclear Factor-κB (NF-κB) activation. TWEAK also promotes tubular cell proliferation, however, it induces mesangial and tubular cell apoptosis under proinflammatory conditions [22,23]. Other new factors suspected to play a role in the development of AKI are Angiopoietin-2 (Ang-2) and Pentraxin-3 (PTX3). Ang-2 is a proinflammatory and endothelial barrier-destabilizing mediator in the vessel wall and macrophages, and has been reported to

be a predictor of mortality in patients with dialysis-dependent AKI [24-26]. PTX3 is an acute phase protein located in endothelium and stored in neutrophils and reportedly plays a role in the pathogenesis of ischemic acute kidney injury, although renal protective effects have been described as well [27,28].

Renal replacement therapy

The most commonly applied modalities of RRT are continuous venovenous haemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). In the trials in this thesis CVVH was applied as RRT modality. In CVVH, solutes are removed by convective clearance. Convection occurs when a solution with its content is driven by hydrostatic force across a semipermeable membrane (solvent drag). The crucial element in CVVH, as in all hemodialysis and -filtration techniques, is the artificial kidney or the hemofilter. The hemofilter contains the semipermeable membrane across which the filtration of solutes and fluid occurs. There are several types of hemofilters with different characteristics and the choice of the filter is of great importance in quality and adequacy of treatment. Filters utilized in CVVH usually have a molecular weight exclusion limit of approximately 50kD. One characteristic of interest when selecting a hemofilter is biocompatibility. Biocompatibility refers to the ability of a material to perform with an appropriate host response in a specific situation. Concerning biocompatibility there are currently three types of membranes manufactured: cuprophane, cellulose acetate and synthetic non-cellulose, with cuprophane considered to be bio*in*compatible and may also be associated with an unfavourable outcome [29]. The volume and solute loss in haemofiltration must be compensated by infusion of a replacement solution with an ideal composition. The replacement solution used can be infused either before (predilution) or after (postdilution) the filter. Predilution CVVH may effectuate less effective clearance, since the blood is diluted before it encounters the filter, however, may increase filter survival compensating the loss of efficacy. In the literature, evidence favouring one method over the other is scarce [30,31].

Anticoagulation

In critically ill patients the main limit in applying CVVH remains the need of anticoagulation in order to minimize the risk of clotting of the extracorporeal circuit. Clotting and the resultant filter down-time adversely affect metabolic control [32]. Excessive anticoagulation, however, may result in bleeding complications reported to occur in 10-50% of treatments [33]. Ideally, anticoagulation is limited to the extracorporeal circuit without affecting the

systemic coagulation. Many anticoagulation methods have been pursued including low dose heparin, low molecular weight heparin (LMWH), prostanoids, mesilates and regional citrate anticoagulation. Heparin remains a commonly used anticoagulant for CRRT. It is easy to use and monitor and provides adequate extracorporeal anticoagulation. The binding to antitrombin gives unfractionated heparin the majority of its anticoagulant property. LMWH predominantly inhibits factor Xa. The major drawback of LMWH is the difficulty to counteract bleeding if it occurs. The hazards of systemic anticoagulation such as bleeding and development of heparin-induced thrombocytopenia (HIT) are major drawbacks of all forms of heparin. CItrate has the ability to deliver the anticoagulation regionally. It acts as an anticoagulant by its ability to chelate calcium, needed in activation of several clot factors (II, V, VII, VIII, IX, X, XIII) and in the conversion of fibrinogen to fibrin.

Citrate anticoagulation in CVVH

There are several citrate-based solutions available with different citrate-concentrations. Citrate is infused prefilter as a separate trisodium citrate or acid-citrate-dextrose solution, or is incorporated in the replacement fluid. In case of a high concentration citrate solution, also known as hypertonic citrate solution because of the high sodium content of trisodium citrate, citrate is administered prefilter together with the use of hypotonic alkali-free replacement solution or dialysate to prevent the main metabolic hazards of this method, being hypernatremia and/or metabolic alkalosis. Alternatively, citrate can be incorporated in the isotonic replacement fluid, the method used in this thesis. By administering citrate pre-filter, complete anticoagulation of the extracorporeal circuit will be allowed (Fig. 1).

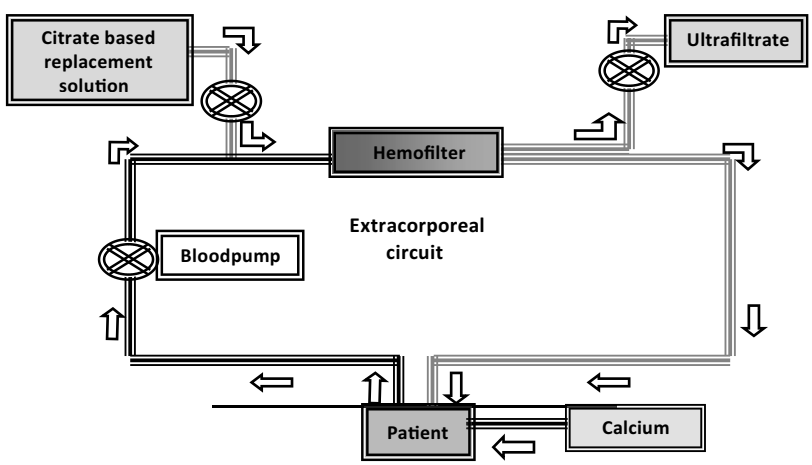

Figure 1 Schematic representation of predilution citrate-CVVH

Table 2 Randomized controlled trials: citrate in CRRT

Adapted from Wu et al. [33] (reproduced with permission)

Study	Number of patients	Age (yrs)	Disease severity
Monchi et al. 2004; BE [40]	C: 8 H: 12	C: 67 (52-77)[b] H: 64 (52-74)[b]	C: 40 (31-53)[b] (SAPS) H: 42 (33-55)[b] (SAPS)
Kutsogiannis et al. 2005; CA [42]	C: 16 H: 14	C: 66.5 ± 14.5 H: 63.9 ± 21.2	C: 7.75 ± 3.53 (OD) H: 9.42 ± 2.31 (OD)
Betjes et al. 2007; NL [43]	C: 21 H: 27	C: 57.8 ± 4.2[a] H: 55.2 ± 2.8[a]	C: 51.4 ± 4.1 (SAPS) H: 51.0 ± 2.6[a] (SAPS
Fealy et al. 2007; AU [44]	C: 10 H: 10	71 (63.5-76.5)[b]	SAPS: 41 (31-43)[b]; APACHE: 17 (15-21)[b]
Oudemans-van Straaten et al. 2009; NL [45]	C: 97 H: 103	C: 73 (67-79)[b] N: 73 (64-79)[b]	C: 59 (55-62)[b] (SAPS); 28 (27-30) (APACHE) N: 61 (58-64)[b] (SAPS); 28 (27-29) (APACHE)
Hetzel et al. 2011; DE [46]	C: 87 H: 83	C: 61.72 ± 15.29 H: 65.11 ± 12.46	C: 21.8 ± 5.1 (APACHE); 9.95 ± 2.9 (SOFA) H: 22.04 ± 5.5 (APACHE); 9.95 ± 2.6 (SOFA)

Note: Values are presented as mean ± standard deviation unless noted otherwise.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation II; aPTT, activated partial thromboplastin time; AU, Australia; BE, Belgium; BW, body weight; C, citrate; CA, Canada; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous haemofiltration; CVVHDF, continuous venovenous hemodiafiltration; DE, Germany; H, heparin; HF, haemofiltration; iCa, ionized calcium; N, nadroparin; NL, the Netherlands; OD, logistic organ dysfunction score; SAPS, Simplified Acute Physiology II score; SOFA, Sepsis-Related Organ Failure Assessment score.
[a]Mean ± standard error. [b]Median (interquartile range).

	Intervention	Modality; Dilution; blood flow	Filter survival (hrs)	Bleeding episodes	Mortality
	C: Trisodium citrate administered at starting rate of 4.3 mmol/L of extracorporeal blood flow H: Systemic, bolus of 2,000-5,000 U; maintenance of 1,000 U/h, adjusted at 500-2,000 U/h to keep aPTT 60-80 s	CVVH; postdilution; 175 mL/min	C: 70 (44-140) H: 40 (17-48)	C: 0 H: 1	No data
	C: Regional trisodium citrate titrated to maintain post-hemofilter iCa = 0.25-0.35 mmol/L H: Systemic, bolus of 50 U/kg for aPTT = 35 s; maintenance protocol to keep aPTT at 45-65 s	CVVHDF; predilution; 125 mL/min	C: 124.5 (95-157)[b] H: 38.3 (24.8-62)[b]	C: 0 H: 7	ICU/hospital discharge C: 13/16 (84%) H: 10/14 (71%)
	C: Regional trisodium citrate 13%, 55 mL/min; postfilter iCa = 0.25-0.35 mmol/L H: Bolus of 3,000-5,000 IU, based on weight and aPTT	CVVH; postdilution; 150 mL/min	C: 36.0 H: 38.4	C: 0 H: 10	No data
	C: Regional citrate-based replacement fluid 14 mmol/L; iCa =1.1-1.3 mmol/L H: Regional prefilter at 1,500 IU/h and protamine postfilter at 15 mg/h	CVVH; predilution; 150 mL/min	C: 17 (12-19.5) H: 13 (9-28)	C: 0 H: 0	No data
	C: Citrate dose was 3 mmol/L blood flow N: Systemic, bolus of 2,850 IU/h; maintenance of 380 IU/h; BW ±100 kg: 3,800 IU at initial, followed by 456 IU/h	CVVH; postdilution; 220 mL/min	C: 27 (13-47) H: 26 (5-43)	C: 6 H: 16	3-months C: 43% (31-51) H: 57 % (48-67)
	C: 21.8 ±5.1 (APACHE); 9.95 ± 2.9 (SOFA) H: 22.04 ±5.5 (APACHE); 9.95 ± 2.6 (SOFA)	CVVH; predilution; 3x HF-solution flow mL/min	C: 37.5 ± 23[a] H: 26.1 ± 19[a]	C: 4 H: 7	30 days C: 47% H: 41%

An ionized calcium concentration below 0.35 mmol/l is required to inhibit coagulation. The anticoagulant effect of citrate is overwhelmed and neutralized when a relatively small volume of citrated blood of the extracorporeal circuit returns and mixes with central venous blood containing relatively large amounts of calcium. Therefore, citrate can be used as regional anticoagulant, without systemic anticoagulation. The tricarboxylic acid pathway in the liver, skeletal muscles and renal cortex clears citrate and subsequently bicarbonate is produced. The metabolism of 1 mole of citrate will generate 3 moles of bicarbonate. Citrate carries the risk of hypocalcemia when it is insufficiently metabolized and thus accumulates. Also, metabolic acidosis may develop when citrate is insufficiently metabolized, while metabolic alkalosis develops when too much citrate enters the circulation and is subsequently metabolized to bicarbonate. Moreover, when calcium-free replacement fluids are used, calcium supplementation is required. In terms of safety monitoring, low systemic ionised calcium and metabolic alkalosis are the main potential complications and in order to prevent these complications, the anion gap, total to ionised calcium ratio and blood gasses are measured at least four times daily during CRRT with a citrate based anticoagulant regime. Citrate has been successfully adapted for use in continuous renal replacement therapies [34-39]. Several clinical trials comparing heparin to citrate for CVVH in critically ill patients have been published, yet most with small patient numbers and mainly focussing on filter survival times, with varying results [40-44, Table 2]. Concentrated citrate in postdilutional CVVH reduced mortality as compared to low molecular weight heparin in a study by Oudemans et al, which could only be partly explained by less bleeding. Since the reduction occurred particularly in septic patients and patient with a high degree of organ failure, improved biocompatibility for citrate as compared to heparin-based CVVH is suggested [45]. Hetzel et al., however, compared unfractionated heparin to citrate in predilutional CVVH and did not find a survival benefit for citrate [46]. Two meta analyses on this topic showed no difference in mortality. However, citrate reduced the risk of bleeding and was more efficacious in one of them [33,47]. It therefore remains to be elucidated which anticoagulation strategy is superior on major endpoints in the critically ill patients with AKI.

Replacement solution

The replacement solution in CVVH consists of balanced electrolyte solutions that closely resemble the composition of the ultrafiltrate minus the waste products. They may contain sodium, glucose, chloride, magnesium, calcium and some potassium. The solutions also contain a buffer to correct for the metabolic acidosis and convective loss of bicarbonate.

Buffers used are bicarbonate, lactate, acetate or citrate. The composition of the different replacement fluids used in this thesis are shown in Table 3. Since for predilutional citrate-CVVH a custom-made citrate-containing replacement solution was used, the solution was free of calcium.

Table 3 Composition of replacement fluids used in this thesis

	Bicarbonate HF 32 BIC	**Citrate HF CitPre**	**Lactate BH 504**
Sodium (mmol/L)	140	139.9	140
Potassium (mmol/L)	2.0	3.0	1.5
Magnesium (mmol/L)	0.5	0.5	0.5
Calcium (mmol/L)	1.75		1.5
Chloride (mmol/L)	111.5	104	103
Glucose (mmol/L)	1	5	11.1
Citrate (mmol/L)	–	13.3	–
Bicarbonate (mmol/L)	32	–	–
Lactate (mmol/L)	3	–	42

Biocompatibility and anticoagulation

Biocompatibility and anticoagulation may be closely related as the type of anticoagulation might affect the biocompatibility of the hemofilter. Bioincompatibility can be defined as incompatibility with living tissue and on this topic best described by an inflammatory response to various components of CVVH [48,49], including complement activation and C5a release followed by polymorphonuclear cell degranulation with release of intracellular products such as elastase, myeloperoxidase (MPO), NGAL and TWEAK. Interestingly, Oudemans et al. found citrate to reduce mortality particulary in septic patients or patients with a high degree of organ failure, suggesting a role of citrate in the metabolism of inflammation [45]. Indeed, regional citrate anticoagulation could down regulate the release of pro-inflammatory mediators caused by the blood-hemofilter interaction by creating an almost calcium-free environment in the extracorporeal circuit. Calcium signaling may contribute to activation of NFκB and subsequent release of pro-inflammatory mediators like interleukin-6 (IL-6) and -8 (IL-8) from mononuclear cells. Moreover, as demonstrated in intermittent hemodialysis and in blood in vitro, citrate may lower polymorphonuclear cell degranulation as observed with heparin; this may be partly independent of complement activation since cations, such as calcium, may be pivotal in cell activation and degranulation [50-57].

Removal of mediators of inflammation by CRRT

A postulated benefit of CVVH, apart from improved metabolic control, is the removal of harmful cytokines released from the circulation during sepsis and AKI by convection or absorption by the filter [59-61]. However, the magnitude and significance of this potential removal is highly debated and may depend on underlying diseases, size and baseline levels of mediators, hemofilter properties and other factors like the anticoagulants used [62-73]. In theory, high-volume haemofiltration (HVHF) with frequent filter change has the potential of removal of inflammatory mediators, however, a recent trial showed no superiority in terms of reduction of mortality or organ function for HVHF when compared to contemporary treatment [74].

Outline of the thesis

The general aim of this thesis is to contribute to the search for the best anticoagulation regimen for CVVH in AKI. We explore the differences between regional citrate anticoagulation and systemic heparin anticoagulation in terms of efficacy and patient survival. Furthermore, we focus on biocompatibilty of the two anticoagulation regimens when applied in CVVH as compared to CVVH without anticoagulation. The effects of citrate on hemostatic and on inflammatory markers are analysed.

We hypothesize that regional citrate anticoagulation is a safe and efficient anticoagulant in critically ill patients with AKI requiring CVVH and favours renal and patient outcomes when compared to unfractionated heparin. We therefore compare citrate to heparin in CVVH in terms of mortality and renal outcome in a multi-centered randomized controlled trial in **chapter 2**. Secondary endpoints are safety and efficacy. Additionally, a cost analysis for the first 72 hours of prescribed CVVH is performed.

We study the effect of citrate and heparin as compared to no anticoagulation on hemostatic and inflammatory markers in CVVH in chapters 3-7. Firstly, our hypothesis is that by the chelation of calcium by citrate, the release of interleukines by monocytes is reduced. Therefore, we compare systemic IL-6 and IL-8 levels in CVVH and their clearance in the different anticoagulation methods in **chapter 3**. In addition, we hypothesize that by creating a calcium-free environment in the filter with citrate, the degranulation of neutrophils will occur less, favouring this anticoagulation method over heparin. We study the release of neutrophil degranulation products elastase and MPO, and C5a release during CVVH in **chapter 4**. Furthermore, we hypothesize that C5a, based on its molecular size, will be cleared

from the plasma of patients when undergoing CVVH. Based on similar principles, in **chapter 5** we hypothesize that the potential release of the AKI biomarker NGAL by neutrophils in the hemofilter will be less in citrate-CVVH than heparin-CVVH and that NGAL, based on molecular size will be cleared by CVVH. We aim to explore whether its value as a biomarker is thus affected. Likewise, in **chapter 6**, plasma levels of novel mediators of AKI, TWEAK, Ang-2 and PTX3, are studied over time during citrate and heparin CVVH. Since superior filter survival times have been proposed for citrate-based CVVH as compared to heparin, we hypothesize that there are differences in coagulation and inhibition of coagulation during CVVH between the aforementioned anticoagulation regimens. The aim of **chapter 7** is to explore the mechanisms possibly responsible for improved filter survival times in citrate-CVVH.

Chapter 8 contains the summary and future perspectives.

References

1. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med. 2006;34:1913-1917
2. Hoste EA, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, Kellum JA. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10:R73
3. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care. 2004;8:R204-212
4. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, et al. (2007) Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11: R31
5. de Mendonça A, Vincent JL, Suter PM, Moreno R, Dearden NM, Antonelli M, Takala J, Sprung C, Cantraine F. Acute renal failure in the ICU: risk factors and outcome evaluated by the SOFA score. Intensive Care Med. 2000;26:915-921
6. Metnitz PG, Krenn CG, Steltzer H, Lang T, Ploder J, Lenz K, Le Gall JR, Druml W. Effect of acute renal failure requiring renal replacement therapy on outcome in critically ill patients. Crit Care Med. 2002;30:2051-2058
7. Uchino S, Kellum JA, Bellomo R, Doig GS, Morimatsu H, Morgera S, Schetz M, Tan I, Bouman C, Macedo E, Gibney N, Tolwani A, Ronco C. Acute renal failure in critically ill patients: a multinational, multicenter study. JAMA. 2005;17;294:813-818
8. Kjeldsen L, Bainton DF, Sengeløv H, Borregaard N: Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. Blood 1994, 83:799-807
9. Paragas N, Qiu A, Zhang Q, Samstein B, Deng SX, Schmidt-Ott KM, Viltard M, Yu W, Forster CS, Gong G, Liu Y, Kulkarni R, Mori K, Kalandadze A, Ratner AJ, Devarajan P, Landry DW, D'Agati V, Lin CS, Barasch J: The Ngal reporter mouse detects the response of the kidney to injury in real time. Nat Med 2011;17:216-222
10. Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, Ruff SM, Zahedi K, Shao M, Bean J, Mori K, Barasch J, Devarajan P: Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet 2005;365:1231-1238
11. Kümpers P, Hafer C, Lukasz A, Lichtinghagen R, Brand K, Fliser D, Faulhaber-Walter R, Kielstein JT: Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. Crit Care 2010; 14: R9
12. Cruz DN, de Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, Piccinni P, Ronco C: Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 2010;36:444-451
13. de Geus HR, Bakker J, Lesaffre EM, le Noble JL: Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. Am J Respir Crit Care Med 2011;183:907-914

14. Soto K, Papoila AL, Coelho S, Bennett M, Ma Q, Rodrigues B, Fidalgo P, Frade F, Devarajan P: Plasma NGAL for the Diagnosis of AKI in Patients Admitted from the Emergency Department Setting. Clin J Am Soc Nephrol 2013;8:2053-2063
15. Hjortrup PB, Haase N, Wetterslev M, Perner A: Clinical review: Predictive value of neutrophil gelatinase-associated lipocalin for acute kidney injury in intensive care patients. Crit Care 2013; 17:211
16. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A: Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis 2009;54:1012-1024
17. Bagshaw SM, Bennett M, Haase M, Haase-Fielitz A, Egi M, Morimatsu H, D'amico G, Goldsmith D, Devarajan P, Bellomo R: Plasma and urine neutrophil gelatinase-associated lipocalin in septic versus non-septic acute kidney injury in critical illness. Intensive Care Med 2010;36:452-461
18. Srisawat N, Murugan R, Lee M, Kong L, Carter M, Angus DC, Kellum JA: Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. Kidney Int 2011;80:545-552
19. Mårtensson J, Bell M, Oldner A, Xu S, Venge P, Martling CR: Neutrophil gelatinase-associated lipocalin in adult septic patients with and without acute kidney injury. Intensive Care Med 2010; 36:1333-1340
20. Kim H, Hur M, Cruz DN, Moon HW, Yun YM: Plasma neutrophil gelatinase-associated lipocalin as a biomarker for acute kidney injury in critically ill patients with suspected sepsis. Clin Biochem 2013;46:1414-1418
21. Otto GP, Busch M, Sossdorf M, Claus RA: Impact of sepsis-associated cytokine storm on plasma NGAL during acute kidney injury in a model of polymicrobial sepsis. Crit Care 2013;17:419
22. Sanz AB, Sanchez-Nino MD, Ortiz A. TWEAK, a multifunctional cytokine in kidney injury. Kidney Int 2011;80:708-718
23. Hotta K, Sho M, Yamato I, Shimada K, Harada H, Akahori T, Nakamura S, Konishi N, Yagita H, Nonomura K, Nakajima Y. Direct targeting of fibroblast growth factor-inducible 14 protein protects against renal ischemia reperfusion injury. Kidney Int 2011;79:179-188
24. Kümpers P, Hafer C, David S, Hecker H, Lukasz A, Fliser D, Haller H, Kielstein JT, Faulhaber-Walter R. Angiopoietin-2 in patients requiring renal replacement therapy in the ICU: relation to acute kidney injury, multiple organ dysfunction syndrome and outcome. Intensive Care Med 2010;36:462-470
25. Wulfert FM1, van Meurs M, Kurniati NF, Jongman RM, Houwertjes MC, Heeringa P, Struys MM, Zijlstra JG, Molema G. Age-dependent role of microvascular endothelial and polymorphonuclear cells in lipopolysaccharide-induced acute kidney injury. Anesthesiology 2012;117:126-136
26. Liu KL, Lee KT, Chang CH, Chen YC, Lin SM, Chu PH. Elevated plasma thrombomodulin and angiopoietin-2 predict the development of acute kidney injury in patients with acute myocardial infarction. Crit Care 2014;18:R100.
27. Chen J, Matzuk MM, Zhou XJ, Lu CY. Endothelial pentraxin 3 contributes to murine ischemic acute kidney injury. Kidney Int 2012;82:1195-1207
28. Lech M, Römmele C, Gröbmayr R, Susanti HE, Kulkarni OP, Wang S, Gröne H-J, Uhl B, Reichel C, Krombach F, Garlanda C, Mantovani A, Anders H-J. Endogenous and exogenous pentraxin-3 limits postischemic acute and chronic kidney injury. Kidney Int 2013:83;647-661

29. van Stone JC. The effect of dialyzer membrane and etiology of kidney disease on the preservation of residual renal function in chronic hemodialysis patients. ASAIO J. 1995;41:M713-716
30. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R. Pre-dilution vs. post-dilution during continuous veno-venous haemofiltration: impact on filter life and azotemic control. Nephron Clin Pract 2003;94:c94-98
31. van der Voort PH, Gerritsen RT, Kuiper MA, Egbers PH, Kingma WP, Boerma EC. Filter run time in CVVH: pre- versus post-dilution and nadroparin versus regional heparin-protamine anticoagulation. Blood Purif 2005;23:175-180
32. Uchino S, Fealy N, Baldwin I, Morimatsu H, Bellomo R: Continuous is not continuous: the incidence and impact of circuit “down-time” on uraemic control during continuous veno-venous haemofiltration. Intensive Care Med 2003;29:575-578
33. Wu MY, Hsu YH, Bai CH, Lin YF, Wu CH, Tam KW: Regional citrate versus heparin anticoagulation for continuous renal replacement therapy: a meta-analysis of randomized controlled trials. Am J Kidney Dis 2012;59:810-818
34. Mehta RL, McDonald BR, Aguilar MM, Ward DM: Regional citrate anticoagulation for continuous arteriovenous hemodialysis in critically ill patients. Kidney Int 1990;38:976-981
35. Mehta RL, McDonald BR, Ward DM: Regional citrate anticoagulation for continuous arteriovenous hemodialysis. Contrib Nephrol 1991;93:210-214
36. Palsson R, Niles JL : Regional citrate anticoagulation in continuous venovenous haemofiltration in critically ill patients with a high risk of bleeding. Kidney Int 1999;55:1991-1997
37. Kutsogiannis DJ, Mayers I, Chin WD, Gibney RT: Regional citrate anticoagulation in continuous venovenous hemodiafiltration. Am J Kidney Dis 2000;35:802-811
38. Tolwani AJ, Campbell RC, Schenk MB, Allon M, Warnock DG: Simplified citrate anticoagulation for continuous renal replacement therapy. Kidney Int 2001;60:370-374
39. Gabutti L, Marone C, Colucci G, Duchini F, Schönholzer C: Citrate anticoagulation in continuous venovenous hemodiafiltration: a metabolic challenge. Intensive Care Med 2002;28:1419-1425
40. Monchi M, Berghmans D, Ledoux D, Canivet JL, Dubois B, Damas P: Citrate vs. heparin for anticoagulation in continuous venovenous haemofiltration: a prospective randomized study. Intensive Care Med 2004;30:260-265
41. Bagshaw SM, Laupland KB, Boiteau PJ, Godinez-Luna T: Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. J Crit Care 2005;20:155-161
42. Kutsogiannis DJ, Gibney RT, Stollery D, Gao J: Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. Kidney Int 2005;67:2361-2367
43. Betjes MG, van Oosterom D, van Agteren M, van de Wetering J: Regional citrate versus heparin anticoagulation during venovenous haemofiltration in patients at low risk for bleeding: similar hemofilter survival but significantly less bleeding. J Nephrol 2007;20: 602-608
44. Fealy N, Baldwin I, Johnstone M, Egi M, Bellomo R. A pilot randomized controlled crossover study comparing regional heparinization to regional citrate anticoagulation for continuous venovenous haemofiltration. Int J Artif Organs. 2007;30:301-307

45. Oudemans-van Straaten HM, Bosman RJ, Koopmans M, van der Voort PH, Wester JP, van der Spoel JI, Dijksman LM, Zandstra DF: Citrate anticoagulation for continuous venovenous haemofiltration. Crit Care Med 2009;37:545-552
46. Hetzel GR, Schmitz M, Wissing H, Ries W, Schott G, Heering PJ, Isgro F, Kribben A, Himmele R, Grabensee B, Rump LC: Regional citrate versus systemic heparin for anticoagulation in critically ill patients on continuous venovenous haemofiltration: a prospective randomized multicentre trial. Nephrol Dial Transplant 2011;26:232-239
47. Zhang Z, Hongying N: Efficacy and safety of regional citrate anticoagulation in critically ill patients undergoing continuous renal replacement therapy. Intensive Care Med 2012;38: 20-28
48. Cheung AK: Biocompatibility of hemodialysis membranes. J Am Soc Nephrol. 1990;1: 150-161
49. Grooteman MP, Gritters M, Wauters IM, Schalkwijk CG, Stam F, Twisk J, Ter Wee PM, Nubé MJ: Patient characteristics rather than the type of dialyser predict the variability of endothelial derived surface molecules in chronic haemodialysis patients. Nephrol Dial Transplant. 2005;20:2751-2758
50. Léculier C, Couprie N, Adeleine P, Leitienne P, Francina A, Richard M: The effects of high molecular weight- and low molecular weight-heparins on superoxide ion production and degranulation by human polymorphonuclear leukocytes. Thromb Hemost. 1993;69:519-531
51. Böhler J, Schollmeyer P, Dressel B, Dobos G, Hörl WH: Reduction of granulocyte activation during hemodialysis with regional citrate anticoagulation: dissociation of complement activation and neutropenia from neutrophils degranulation. J Am Soc Nephrol. 1996;7: 234-241
52. Bos JC, Grooteman MP, van Houte AJ, Schoorl M, van Limbeek J, Nubé MJ: Low polymorphonuclear cell degranulation during citrate anticoagulation: a comparison between citrate and heparin dialysis. Nephrol Dial Transplant. 1997;12:1387-1393.
53. Leitienne P, Fouque D, Rigal D, Adeleine P, Trzeciak M-C, Laville M: Heparins and blood polymorphonuclear stimulation in haemodialysis: an expansion of the biocompatibility concept. Nephrol Dial Transplant. 2000;15:1631-1637
54. Gritters M, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, Scheffer PG, Teerlink T, Schalkwijk CG, Spreeuwenberg M, Nubé MJ: Citrate anticoagulation abolishes degranulation of polymorphonuclear cells and platelets and reduces oxidative stress during haemodialysis. Nephrol Dial Transplant. 2006;21:153-159
55. Gritters M, Borgdorff P, Grooteman MP, Schoorl M, Schoorl M, Bartels PC, Tangelder GJ, Nubé MJ: Reduction in platelet activation by citrate anticoagulation does not prevent intradialytic hemodynamic instability. Nephron Clin Pract. 2007;106:c9-16
56. Scheffer PG, van der Zwan LP, Schindhelm RK, Vermue HP, Teerlink T: Myeloperoxidase concentrations in EDTA-plasma of healthy subjects are discordant with concentrations in heparin plasma and serum. Clin Biochem. 2009;42:1490-1492
57. Tiranathanagul K, Jearnsujitwimol O, Susantitaphong P, Kijkriengkraikul N, Leelahavanichkul A, Srisawat N, Praditpornsilpa K, Eiam-Ong S: Regional citrate anticoagulation reduces polymorphonucelar cell degranulation in critically ill patients treated with continuous venovenous haemofiltration. Ther Apher Dial. 2011;15:556-564

58. Marshall CJ, Nallaratnam M, Mocatta T, Smyth D, Richards M, Elliott JM, Blake J, Winterbourn CC, Kettle AL, McClean DR: Factors influencing local and systemic levels of plasma myeloperoxidase in ST segment elevation acute myocardial infarction. Am J Cardiol. 2010;106:316-322
59. Bouman CSC, van Olden RW, Stoutenbeek CP. Cytokine filtration and adsorption during pre- and postdilution haemofiltration in four different membranes. Blood Purif 1998;16:261–268
60. Cole L, Bellomo R, Davenport P, Tipping P, Ronco C. Cytokine removal during continuous renal replacement therapy: an ex vivo comparison of convection and diffusion. Int J Artif Org 2004;27:388–397
61. Rimmelé T, Kellum JA. Clinical review: blood purification for sepsis. Crit Care 2011;15:205
62. Peng Z, Pai P, Hong-Bao L, Rong L, Han-Min W, Chen H. The impacts of continuous veno-venous haemofiltration on plasma cytokines and monocyte human leukocyte antigen-DR expression in septic patients. Cytokine 2010;50:186–191
63. Bellomo R, Tipping P, Boyce N. Interleukin-6 and interleukin-8 extraction during continuous venovenous hemodiafiltration in septic acute renal failure. Renal Fail 1995;17:457–466
64. Hoffmann JN, Hartl W, Deppisch R, Faist E, Jochum M, Inthorn D. Haemofiltration in human sepsis: evidence for elimination of immunomodulatory substances. Kidney Int 1995;48: 1563–1570
65. Sander A, Armbruster W, Sander B, Daul AE, Lange R, Peters J. Haemofiltration increases IL-6 clearance in early systemic inflammatory response syndrome but does not alter IL-6 and TNF-a plasma concentrations. Intens Care Med 1997;23:878–884
66. Sanchez-Izquierdo Ropera JA, Perz Vela JL, Lozano Quintana MJ, Alted Lopez E, Ortuñode Solo B, Ambros Checa A. Cytokines clearance during venovenous haemofiltration in the trauma patient. Am J Kidney Dis 1997;30:483–488
67. Heering P, Morgera S, Schmitz FJ, Schmitz G, Willers R, Schultheiss HP, et al. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous haemofiltration. Intens Care Med 1997;23:288–296
68. Koperna T, Vogl SE, Pöschl GP, Hamilton G, Röder G, Germann P. Cytokine patterns in patients who undergo haemofiltration for treatment of multiple organ failure. World J Surg 1998;22:443–448
69. Kellum JA, Johnson JP, Kramer D, Palevsky P, Brady JJ, Pinsky MR. Diffusive vs convective therapy: effects on mediators of inflammation in patients with severe systemic inflammatory response syndrome. Crit Care Med 1998;26:1995–2000
70. De Vriese AS, Colardyn FA, Philipp JJ, Vanholder RC, De Sutter JH, Lameire NH. Cytokine removal during continuous haemofiltration in septic patients. J Am Soc Nephrol 1999;10: 846–853
71. Sieberth H-G, Kierdorf HP. Is cytokine removal by continuous haemofiltration feasible? Kidney Int 1999;56:S79–83
72. Klouche K, Cavadore P, Portales P, Clot J, Canaud B, Béraud JJ. Continuous venovenous haemofiltration improves hemodynamics in septic shock with acute renal failure without modifying TNFa and IL-6 plasma concentrations. J Nephrol 2002;15:150–157
73. Hirano T, Hirasawa H, Oda S, Shiga H, Nakanishi K, Matsuda K, et al. Modulation of polymorphonucelar leukocyte apoptosis in the critically ill by removal of cytokines with continuous hemodiafiltration. Blood Purif 2004;22:188–197